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# Pathophysiology of obstructive nephropathy

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## Case presentation

A 56-year-old black woman was admitted to Barnes Hospital for evaluation of acute renal failure. Seven months earlier, evaluation for lower abdominal pain disclosed an abnormal Pap smear. Frozen section of a cervical biopsy obtained during a dilatation and curettage 6 months prior to admission was diagnosed as "invasive squamous cell carcinoma." At that time a purulent cervical discharge was noted. Three days after the biopsy was performed, the patient had a total abdominal hysterectomy at a local hospital. Multiple adhesions were found in the pelvis, but there was no evidence of tumor. Although radiation therapy was recommended, the patient refused further treatment. She was discharged one week after the operation.

The patient was readmitted to the same hospital 2 months prior to admission to Barnes Hospital for a hemorrhoidectomy. At that time the serum creatinine was 1.3 mg/dl and the BUN was 8 mg/dl. The hemorrhoidectomy was performed under general anesthesia. Postoperatively the serum creatinine was 2.0 mg/dl and the BUN was 13 mg/dl. The patient was readmitted to the same hospital 2 weeks prior to admission to Barnes for evaluation of lower extremity edema and tenderness; deep venous thrombosis was suspected, but a venogram was not done. A ventilation/perfusion scan was interpreted as "intermediate probability" for pulmonary embolus, and the patient was treated with heparin and coumadin. Laboratory data during this admission included: hemoglobin, 8.9 g/dl; hematocrit, 28%; white blood cell count, 12,700/mm$^3$; BUN, 26 mg/dl; and serum creatinine, 3.3 mg/dl. Serum potassium on admission was 5.8 mEq/liter. The patient was transfused with 2 units of blood, but no additional laboratory studies were performed until 2 weeks later. At that time the BUN was 77 mg/dl, the serum creatinine was 13.4 mg/dl, and the serum potassium was 7.9 mEq/liter. The patient was treated with Kayexalate and was transferred to Barnes Hospital.

On admission, the patient was poorly responsive. Blood pressure was 130/80 mm Hg (recumbent) without orthostatic change. Pulse was 80/min and regular. Respiratory rate was 16/min. She had presacral edema and a protuberant nontender abdomen. She was lethargic and oriented only to person. Cranial nerves were intact and neither asterixis nor hyperreflexia was present. Pelvic examination revealed a large mass near the cervix with a suggestion of erosion into the rectum. The stool was guaiac positive. Laboratory data on admission revealed: sodium, 130 mEq/liter; potassium, 5.4 mEq/liter; chloride, 100 mEq/liter; bicarbonate, 14.5 mEq/liter; creatinine, 14.8 mg/dl; and glucose, 90 mg/dl. The BUN was 74 mg/dl; uric acid, 14 mg/dl. Serum phosphate was 7.4 mg/dl. Blood gases obtained while the patient was breathing room air revealed: pH, 7.31; $PCO_2$, 32 mm Hg; $PO_2$, 92 mm Hg. Urine potassium was 12 mEq/liter; chloride, 78 mEq/liter; sodium, 92 mEq/liter; and urinary osmolality, 248 mOsm/kg. Results of the urinalysis revealed a specific gravity of 1.005 and more than 20 white cells per high-power field; a dipstick test for occult blood was positive. Hemoglobin was 7.9 g/dl, hematocrit was 23% with a mean corpuscular volume of 81, and the white blood cell count was 10,300 mm$^3$ with a normal differential. Prothrombin time was 35 seconds; partial thromboplastin time was 96 seconds. Abdominal sonogram showed the right kidney to be approximately 12 cm in length and the left kidney to be slightly smaller. The collecting system was mildly dilated on the left and mildly to moderately dilated on the right. An echocardiogram demonstrated no pericardial effusion. Sonogram of the pelvis demonstrated a 3 to 4 cm pelvic mass extending from the midline to the left, deforming the posterior wall of the bladder. On the day after admission cystoscopy demonstrated a large mass infiltrating the trigone of the bladder. Severe edema precluded identification of either ureteral orifice. Simultaneous pelvic examination demonstrated fixation and increased firmness of the superior and anterior aspects of the vagina. Two days after admission, a right percutaneous nephrostomy tube was inserted. An antegrade pyelogram revealed marked stenosis of the distal right ureter that appeared to be the result of an extrinsic mass. After insertion of the nephrostomy tube, the patient had a brisk diuresis, and the serum creatinine fell to 1 mg/dl over the next few days (Table 1). Her serum electrolytes also returned toward normal, as did her mental status.

A CT scan obtained on the third day of hospitalization revealed a large cervical mass causing obstruction of both ureters and invading the bladder. Persistent enlargement of the right ureter was noted. In addition, the left ureter and both kidneys were enlarged, and a density seen in the pericaval region was thought to represent retroperitoneal adenopathy. Vaginal cytology showed epidermoid carcinoma.

The patient was transferred to the gynecologic oncology service 2 weeks after admission and was treated with pelvic and periaortic x-ray therapy and intrapelvic radiation implants. Shortly after discharge she was still anemic and had persistent blood loss from her gastrointestinal tract, but otherwise she was stable and was tolerating therapy well.

## Discussion

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**Table 1.** Laboratory findings in patient under discussion

| Hospital day | 1 | 2 | 3[a] | | 4 | | 5 | | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | A.M. | P.M. | A.M. | P.M. | A.M. | P.M. | | | | | | | |
| Plasma | | | | | | | | | | | | | | | |
| Sodium, *mEq/liter* | 130 | 129 | 130 | 130 | 137 | | 132 | 133 | 133 | 133 | 134 | 134 | 136 | 138 | 141 |
| Potassium, *mEq/liter* | 5.4 | 5.4 | 4.5 | 4.6 | 4.0 | | 6.2 | 4.2 | 3.9 | 4.5 | 4.4 | 4.8 | 5.0 | 4.2 | 3.8 |
| Chloride, *mEq/liter* | 100 | 100 | 96 | | 105 | | 101 | 100 | 101 | 105 | 106 | 107 | 106 | 103 | 106 |
| *Total* $CO_2$, *mEq/liter* | 15 | 15 | 18 | 16 | 20 | | 23 | 21 | 20 | 16 | 20 | 21 | 19 | 24 | 26 |
| Calcium, *mg/dl* | 9.4 | | | | 10.1 | 9.4 | 8.7 | | | 9.3 | | 9.0 | 9.9 | | |
| Phosphorus, *mg/dl* | 7.4 | | | | 4.3 | 3.3 | 2.0 | | | 1.9 | | | 1.7 | | |
| Magnesium, *mg/dl* | 1.9 | | | | | | 0.7 | | | 0.8 | 1.1 | | 1.1 | 1.1 | |
| Creatinine, *mg/dl* | 14.7 | 14.8 | 15 | | 8.3 | 5.9 | 4.6 | 2.9 | 2.2 | 1.4 | 1.5 | 1.4 | 1.5 | 1.5 | 1.4 |
| BUN, *mg/dl* | 74 | 74 | | | 41 | | 15 | | | 8 | | 8 | | | |
| Uric acid, *mg/dl* | 14.0 | | | | 7.9 | | 4.7 | | | | | | | | |
| Hemoglobin, *g/dl* | 7.9 | | 8.0 | | 8.6 | | 7.7 | | 9.2 | 9.2 | | | | 7.4 | 7.4 |
| Urine | | | | | | | | | | | | | | | |
| Volume, *ml/24 hr* | | 750 | | | 8560 | | 11,600 | | 7965 | 7800 | 7225 | 6470 | | | |
| Sodium, *mEq/liter* | | 92 | | | 113 | | 160 | | 143 | 139 | 140 | 180 | 168 | 110 | |
| Potassium, *mEq/liter* | | 12 | | | 7 | | 11.0 | | 9 | | 8 | <10 | 14 | 10 | 11 |
| Chloride, *mEq/liter* | | 78 | | | 91 | | 106 | | 99 | | | | 143 | | |
| Creatinine, *mg/dl* | | 34 | | | | | 16.0 | | 16 | | | 20 | | | |

[a] Right nephrostomy was performed on this day.

*St. Louis, Missouri):* This patient's course illustrates well the untoward effects of urinary tract obstruction on renal function. The functional and biochemical alterations occurring in the kidney as a consequence of urinary tract obstruction have been referred to as obstructive nephropathy [1]. In humans, the effects of urinary tract obstruction on renal function are diverse. Not only are there marked reductions in renal blood flow and glomerular filtration rate, but obstructive nephropathy also can produce significant changes in the reabsorption of a variety of solutes and water in the renal tubule [1–3]. Partial chronic obstruction of the urinary tract can lead to progressive atrophy and destruction of nephrons and can result in chronic renal insufficiency [1]. On the other hand, complete obstruction occurring suddenly results in acute renal failure [1–3]. Because obstruction generally is a remediable cause of kidney failure, early and accurate diagnosis and prompt implementation of appropriate therapeutic maneuvers assume considerable importance in the preservation and restoration of renal function.

The clinical manifestations of urinary tract obstruction are varied. Complete obstruction to urine flow is manifested as anuria. Partial obstruction has a varied presentation, which can include fluctuating urine output, alternating from oliguria to polyuria; urinary tract infection, usually refractory to treatment; abdominal pain; or unexplained acute or chronic renal failure. Obstruction always must be included in the differential diagnosis of acute renal failure, especially when urine output changes rapidly or anuria occurs suddenly.

In the last decade, we have made considerable progress in understanding the mechanisms by which urinary tract obstruction affects renal function. Clinical observations have suggested which of the many functions of the kidney are affected and how much recovery can be expected after a certain period of obstruction [1–5]. Detailed insight into the mechanisms by which obstruction affects renal function has come mainly from laboratory investigations, however [6–8]. Most experimental information regarding the consequences of obstruction on renal function has been obtained in the rat or dog with acute and complete unilateral or bilateral ureteral obstruction, and I should point out that only a few studies have been carried out in experimental models with partial and chronic obstruction of the urinary tract.

*Effects of urinary tract obstruction on ureteral and intrarenal pressures.* An increase in the intraluminal pressure of the ureter and renal tubules is one of the earliest detectable effects of urinary tract obstruction. The rate of increase of ureteral and intratubular pressure depends on the rate of urine flow at the onset of obstruction. In rats undergoing mannitol diuresis, ureteral and intratubular pressures reached values of approximately 40 mm Hg within 10 to 15 minutes after the onset of obstruction [9, 10]. In animals not receiving diuretics, ureteral pressure rose to approximately 14 mm Hg, and intratubular pressure did not increase at all during this time interval [9, 11]. When dogs were subjected to ureteral obstruction during saline or mannitol diuresis, ureteral pressure reached 50 to 150 mm Hg within 5 to 15 minutes after the onset of obstruction [12, 13]. If the obstruction persists for more than 4 hours, the intratubular pressure begins to decline; if only one ureter is obstructed, intratubular pressure returns to nearly normal (9–15 mm Hg) after 24 hours of obstruction [7, 14–16]. This decline in intratubular pressure can result from a reduction of fluid volume in the tubular system because of decreased glomerular filtration, increased tubular reabsorption, increased capacity of a compliant pelvis, or some combination of these factors. That this decrease in pressure is not due to an increase in compliance and

capacity of the ureter and pelvis alone is indicated by the marked differences in intratubular pressure values after unilateral or bilateral ureteral obstruction. When both ureters are obstructed in experimental animals, intratubular pressure increases to higher levels than when only one ureter is obstructed [7]. In addition, in bilateral ureteral obstruction, the subsequent decline in intratubular pressure does not return the values to normal. Intratubular pressure has been found to be 30 mm Hg, or about 3 times normal values, after bilateral obstruction for 24 hours in rats [15, 17]. Ureteral pressure also remains higher after 24 hours of bilateral ureteral obstruction than after the same period of unilateral obstruction [18]. Pressures similar to those occurring with unilateral obstruction have been found when single nephrons, in an otherwise normal kidney, are obstructed for 24 hours by an oil block [19, 20].

*Effects of obstruction on glomerular filtration rate.* The rate of glomerular filtration is governed by: *(1)* net ultrafiltration pressure across glomerular capillaries; *(2)* permeability of the glomerular capillary wall to water and small solutes; and *(3)* total surface area of the capillaries. The net ultrafiltration pressure represents the difference between the hydrostatic pressure in glomerular capillaries minus the sum of plasma oncotic pressure in glomerular capillaries plus the hydrostatic pressure in Bowman's space [21]. Theoretically, urinary tract obstruction can decrease GFR by affecting one or more of the factors that govern the rate of ultrafiltration across glomerular capillaries. Few studies are available on the effects of continuing obstruction on glomerular filtration rate in humans [22]; however, clinical observations indicate that GRF decreases markedly with high-grade obstruction, and progressive renal failure develops with bilateral obstruction.

In experimental animals, the effects of urinary tract obstruction on GFR have been defined more clearly. Wright measured the so-called proximal tubule stop-flow pressure, an indirect index of glomerular capillary pressure, following the onset of unilateral or bilateral ureteral obstruction in rats [7]. He obtained these values by measuring the pressure in an early segment of the proximal tubule just upstream from an immobile column of viscous oil. As flow stops and glomerular filtration falls to zero, the tubule pressure becomes the difference between glomerular capillary hydrostatic pressure ($P_{gc}$) and oncotic pressure ($\pi_{gc}$), or $P_{SF}$ equals $P_{gc}$ minus $\pi_{gc}$. If filtration is zero, $\pi_{gc}$ remains equal to arterial oncotic pressure, and $P_{SF}$ should vary only with $P_{gc}$. Wright also showed that stop-flow pressure increases in the first 2 to 3 hours following the onset of obstruction to approximately 60 mm Hg in bilateral ureteral obstruction and to about 45 mm Hg in unilateral ureteral obstruction [7]. As with intratubular pressure, glomerular capillary pressure then declines if the obstruction is maintained for more than 4 hours [7]. After 24 hours of obstruction, stop-flow pressure falls to below normal if one ureter is obstructed [7, 16] and to approximately normal if both ureters are obstructed [7, 23]. Similarly, stop-flow measurements indicate that glomerular capillary pressure falls after a single nephron has been obstructed for 24 hours [19, 20]. DalCanton et al suggested that stop-flow pressure under these conditions is a reliable indicator of changes in glomerular capillary pressure [23]. Measuring glomerular capillary pressure directly following the production of obstruction in Munich-Wistar rats with surface glomeruli, the authors found that glomerular capillary pressure rose from 46 to 59 mm Hg after one hour of unilateral ureteral obstruction [23] and then declined to 36 mm Hg after 24 hours of obstruction [16].

The increase in glomerular capillary pressure during the first few hours after the onset of obstruction suggests a decrease in preglomerular resistance, an increase in postglomerular resistance, or a combination of both. An increase in postglomerular resistance would result in a decrease or no change in renal blood flow if preglomerular resistance remains the same. Numerous studies indicate that renal blood flow through the obstructed kidney increases during the first few hours following the onset of obstruction [18, 23–38]. The increase in renal blood flow caused by ureteral obstruction appears limited to the renal cortex. Inner medullary plasma flow decreases from the onset of ureteral obstruction, reaching values about 30% of normal within 6 hours [39]. I will discuss the changes in renal hemodynamics in more detail shortly.

When we consider the forces responsible for ultrafiltration across the glomerular capillaries, it becomes clear that the effects of acute obstruction in decreasing glomerular filtration rate initially arise mainly from an increase in intratubular pressure and hence a decrease in effective filtration pressure (the difference between intraglomerular capillary pressure and the pressure in Bowman's space and/or intratubular pressure). Because, at least in the case of unilateral ureteral obstruction, intratubular pressures and hence pressures in Bowman's space return to normal levels within 24 hours, the decrease in effective ultrafiltration pressure during that period is mainly due to a decrease in hydrostatic pressure in glomerular capillaries. This decrease in glomerular hydrostatic pressure is accompanied by a marked reduction in renal blood flow after 24 hours of obstruction [16, 40, 41]. These data suggest that progressive preglomerular constriction occurs as obstruction persists for more than 5 hours. Various groups have observed that obstruction for 24 hours results in a decrease in total glomerular filtration rate of approximately 80% immediately after the obstruction is relieved [42–44]. Measurements of single-nephron GFR indicate, however, that in surface nephrons, single-nephron GFR decreases by only 60% to 70%, whereas single-nephron GFR in the juxtamedullary units decreases by approximately 50% [44]. These data suggest that there are filtering and nonfiltering nephrons during this period of obstruction, with filtering nephrons exhibiting a decrease in single-nephron GFR. Studies using Hansen's technique to determine the number of filtering nephrons reveal that after 24 hours of unilateral ureteral obstruction, approximately 10% of the surface nephrons and 8% of the juxtamedullary nephrons continue to filter [44]. Filtration was demonstrable 90 minutes after relief of obstruction in approximately 40% of surface nephrons and 33% of juxtamedullary nephrons. By contrast, in the contralateral untouched kidney of these rats, more than 90% of the nephrons were filtering. Consequently, obstruction results in heterogeneous nephron function such that filtration in some units ceases, whereas other nephrons continue to filter but with a decreased glomerular filtration rate [45].

McDougal and Wright demonstrated that the decrease in GFR that occurs with short periods of obstruction, 24 to 36 hours, is completely reversible [46]. These investigators produced urethral obstruction for 30 hours in rats and examined creatinine clearances before and after release of obstruction.

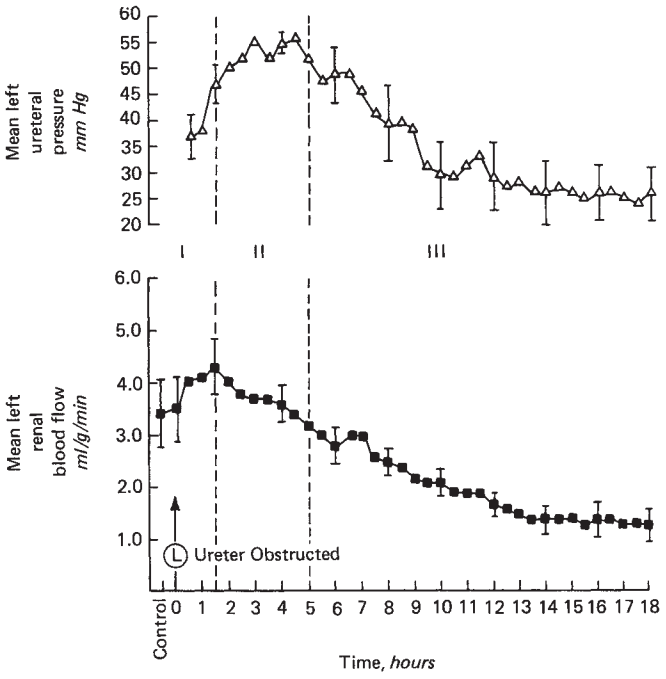


**Fig. 1.** *Triphasic relationship between ipsilateral renal blood flow and left ureteral pressure during 18 hours of left ureteral occlusion (N = 5 ± SE).* In phase I the left renal blood flow and ureteral pressure rise together. In phase II the left renal blood flow begins to decline while the ureteral pressure remains elevated and, in fact, continues to rise. In phase III, the left renal blood flow and ureteral pressure decline together. (From MOODY TE, VAUGHAN ED, GILLENWATER JY: Relationship between renal blood flow and ureteral pressure during 18 hours of total ureteral occlusion, *Investigative Urology,* © by The Williams & Wilkins Co.)

Values for creatinine clearance, which were markedly decreased in the immediate postrelease period, returned to normal approximately one week after the relief of urethral obstruction and were comparable with those obtained in a group of sham-operated rats. These studies thus indicate that the decline in GFR observed with short-term obstruction is completely reversible and that most of the early alterations are functional in nature and do not involve permanent loss of nephrons. By contrast, complete long-term obstruction (more than one week), even if released, leads to permanent loss of renal function, which is greater as the period of obstruction is lengthened [47].

Micropuncture studies have been performed in rats with chronic partial obstruction of one ureter [48, 49]. Ichikawa and Brenner found that after 4 weeks of partial obstruction, total-kidney GFR and single-nephron GFR as well as initial glomerular plasma flow rate in the obstructed kidney were identical to values in the nonobstructed kidney. Nevertheless, glomerular capillary hydrostatic pressure ($P_{gc}$) was significantly higher in obstructed than in nonobstructed kidneys, whereas values for intratubular pressure were similar. Therefore, the mean glomerular transcapillary hydrostatic pressure was significantly higher (by approximately 10 mm Hg) in the experimental kidney, as compared to the contralateral kidney of rats with unilateral ureteral obstruction. Since the other determinants of single-nephron GFR (oncotic pressure and plasma flow) in the obstructed kidney did not differ significantly from those in the contralateral nonobstructed kidney, calculated values for Kf (the factor describing the surface area and permeability characteristics of the filtration membrane) were found to be markedly reduced only in the obstructed kidneys. During infusion of indomethacin or meclofenamate, both inhibitors of prostaglandin synthesis, single-nephron GFR and glomerular plasma flow decreased significantly and arteriolar resistance increased in obstructed kidneys; similar changes were not observed in nonobstructed kidneys [48]. These studies suggest that intrarenal factors, mainly vasodilatory substances such as prostaglandins, antagonize the effects of a simultaneously acting vasoconstrictor which, although not identified, displays the functional properties of angiotensin II. Wilson, using an experimental model similar to that used by Ichikawa and Brenner, noted a mild to moderate reduction in total and single-nephron GFR [49]. This finding might reflect a greater degree of obstruction than that in the studies already described. We should note that Wilson observed distinct atrophy of renal tissue in his animals, whereas Ichikawa and Brenner did not observe any histologic changes.

*Renal hemodynamic alterations.* The renal hemodynamic alterations during acute or chronic urinary tract obstruction contribute significantly to the pathogenesis of obstructive nephropathy. Renal blood flow, after increasing transiently, falls as a function of time after ureteral occlusion. This relationship is not well understood clinically, because the exact time of onset of ureteral obstruction in humans seldom is known. Further, the indirect methods used to measure renal blood flow in humans are affected by declining renal tubular function. In experimental studies, however, the relationship between renal blood flow and the duration of obstruction is clearly defined [40, 41, 50]. In most experimental models with unilateral ureteral obstruction, renal blood flow falls to 50% of control values within 3 to 4 days of obstruction; by the fourth week, renal blood flow decreases to one-third that in the contralateral nonobstructed kidney. The temporal relation between changes in ureteral pressure and renal blood flow has been studied in the dog after complete obstruction of one ureter [28, 29]. The changes observed can be divided into three phases [37] (Fig. 1). During the first phase, renal blood flow actually rises above control values and is associated with a decline in intrarenal resistance. This increase in blood flow occurs during the first 1 to 2 hours after obstruction and is associated with gradually increasing ureteral pressure. In the second phase, approximately 2 to 5 hours after obstruction, renal blood flow declines, returning to control values, while ureteral pressure continues to increase. Finally, in the third phase, ureteral pressure begins to return to control values, but renal blood flow continues to decline and falls progressively with time.

The pathophysiologic mechanism underlying this sequence of events is not completely clear. Two groups have suggested that the initial increase in renal blood flow probably results from augmented production of vasodilatory prostaglandins ($PGE_2$ and prostacyclin) by the obstructed kidney, because administration of prostaglandin synthesis inhibitors (indomethacin, meclofenamate) prevents this increase in renal blood flow [51, 52]. The increased renal prostaglandin production is believed to result from a decline in inner medullary blood flow consequent

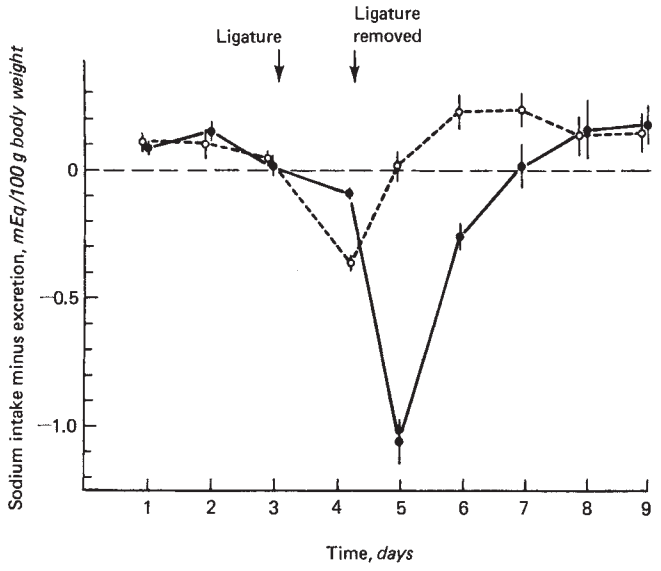


**Fig. 2.** *Changes in external sodium balance, resulting from bilateral obstruction and release* (shaded circles, N = 9) *or from sham operation* (open circles, N = 6) [46].

to the increase in ureteral pressure. The decline in inner medullary blood flow could give rise to an alteration in prostaglandin synthesis, largely in the renal medulla, which in turn results in abrupt changes in vascular resistance and an overshoot in renal blood flow, as in the first phase. The second phase might result in part from an increase in renal resistance, which is the direct effect of increasing ureteral pressure on the interstitium. In the final, chronic phase, an increase in resistance at the preglomerular level is thought to occur. These sequential alterations in renal blood flow and renal resistance explain the initial increase and subsequent fall in intraglomerular hydrostatic pressure.

The mechanisms responsible for the progressive decrease in renal blood flow have not been elucidated. Recent investigations have suggested that increased production of thromboxane $A_2$, a metabolite of arachidonic acid metabolism and a powerful vasoconstrictor, accounts for the decline in blood flow during prolonged obstruction [53, 54]. Conflicting results have been reported in in vivo studies using inhibitors of thromboxane synthesis, however [55, 56]. In our laboratory, administration of OKY-1581, a thomboxane synthesis inhibitor, restored GFR and renal plasma flow only partially in the kidneys of rats with unilateral ureteral obstruction despite the disappearance of thromboxane $B_2$ from the urine (Purkerson ML, Morrison A, and Klahr S, unpublished observations). Persistent renin secretion and angiotensin production also may play a role in the vasoconstriction of chronic obstruction. Failure of saralasin, an antagonist of angiotensin II, to prevent the vasoconstriction of obstruction led Moody et al to conclude that angiotensin is not responsible for the increased vascular resistance that occurs with obstruction [57]. Yarger, Schocken, and Harris found that captopril, an inhibitor of angiotension converting enzyme, increased GFR and renal plasma flow after release of 24-hour unilateral ureteral obstruction. Increased renal nerve activity or high levels of catecholamines at critical sites within the kidney also might contribute to the vasoconstriction of ureteral obstruction [58–60].

*Postobstructive diuresis.* Obstruction of the urinary tract, even after it has been relieved, can significantly alter the kidney's ability to modulate water and solute excretion in response to the homeostatic needs of the body. Indeed, under certain circumstances, a dramatic urinary loss of salt and water can occur following the release of obstruction as it did in the patient under discussion today [61–65]. The mechanisms underlying this syndrome, usually referred to as a postobstructive diuresis, still remain unclear despite extensive research.

Many factors are causally related to this phenomenon. One important factor is the volume status of the patient before the release of obstruction. Individuals who have been given "fluid challenges" in an attempt to characterize the cause of the renal failure, or who have been treated with large quantities of intravenous fluids prior to the release of obstruction, often are volume expanded [66]. Thus, part of the increased urine flow and sodium excretion that occur after release of obstruction is a physiologic response to this expanded state. Another factor is the accumulation, during obstruction, of relatively nonreabsorbable solutes, such as urea, which can promote a solute diuresis and result in high losses of sodium and water after obstruction is relieved [62]. Finally, the inappropriate increase in urine output that occurs after release of obstruction has been thought to result from either an intrinsic defect in renal tubular function or a humoral agent that accumulates during the period of anuria and directly affects sodium and water reabsorption by the renal tubule [67].

Although the relative contribution of each of these factors cannot be clearly elucidated in humans, several animal studies have characterized the pathogenesis of postobstructive diuresis. Figure 2 depicts the changes in external sodium balance before, during, and after bilateral ureteral obstruction in the rat. These studies clearly demonstrate that the increase in sodium and water excretion that occurs following release of obstruction is not merely a physiologic response to volume expansion [46]. This natriuresis and diuresis occur in the presence of a marked decline in GFR and thus must represent a decrease in reabsorption of fluid by at least one, and more likely multiple, anatomic segments of the renal tubule. Micropuncture studies have demonstrated that, after release of acute bilateral ureteral ligation, the amount of water reabsorbed decreases along the proximal and distal tubules of surface nephrons and to the bend of the loop of Henle of deep nephrons [43]. Collecting duct function appeared intact in these studies. That these changes do not result from an increased solute load has been demonstrated in experimental studies in which blood urea concentrations were raised to levels comparable with those achieved during anuria [67]. Sodium and water excretion increased but not to the same magnitude seen following release of obstruction.

Accumulation of natriuretic factors in blood during the interval of complete ureteral obstruction may play a significant role in the ensuing postobstructive diuresis, because a natriuresis and diuresis comparable to those occurring after release of acute bilateral ureteral obstruction can be produced in normal rats by cross-circulation with rats rendered completely obstructed for 24 hours [67]. Further, rats with unilateral ureteral obstruction given a reinfusion of urine from the contralateral kidney develop a marked increase in the excretion of sodium

and water similar in magnitude to that observed after release of bilateral ureteral obstruction [67, 68–70].

On the other hand, a postobstructive diuresis does not occur after release of unilateral ureteral obstruction. Clinical studies of renal function after release of unilateral ureteral obstruction showed that, despite the marked decrease in GFR of the obstructed kidney when compared to the contralateral normal functioning kidney, fractional sodium and water excretion from the postobstructed kidney usually increased [71]. The difference in the magnitude of sodium excretion after bilateral compared to unilateral obstruction seems related to a greater delivery of tubular fluid out of cortical nephrons after release of bilateral obstruction. A number of findings seem to support this conclusion. First, Better et al showed in human studies that phosphate reabsorption in the postobstructed kidney frequently exceeds that in the normal functioning contralateral control [72]. Because phosphate reabsorption is primarily a function of the proximal tubule, these studies suggest increased renal tubular reabsorption of sodium and water in this segment. Second, in micropuncture studies, Buerkert and coworkers found that water and sodium reabsorption along the proximal and distal tubular segment of surface nephrons markedly increases after release of unilateral ureteral obstruction [44] when compared to results obtained in normal hydropenic rats or after release of bilateral ureteral obstruction [43]. Additional micropuncture studies have suggested that the increase in fractional sodium and water excretion after release of unilateral ureteral obstruction results from increased delivery of sodium and water out of deep nephrons [44].

To determine the effects of 24 hours of obstruction on the intrinsic function of different nephron segments, Hanley and Davidson produced unilateral or bilateral ureteral obstruction in the New Zealand white rabbit [73]. After 24 hours, they examined intrinsic nephron function by isolating segments from these obstructed kidneys and determining transport properties by the method of isolated tubule microperfusion. These studies have allowed direct comparison of similar nephron segments from unilaterally and bilaterally obstructed kidneys. In addition, Hanley and Davidson were able to examine segments not directly accessible to micropuncture or papillary microcatheterization. These studies demonstrated that neither unilateral nor bilateral ureteral obstruction decreased fluid reabsorption in the proximal convoluted tubule of surface nephrons. This finding contrasts with micropuncture studies in the rat, which demonstrated decreased fluid reabsorption in this segment in bilateral ureteral obstruction, but not in unilateral ureteral obstruction [43, 44]. Fluid reabsorption decreased in the pars recta of surface nephrons in both unilateral and bilateral ureteral obstruction. In addition, fluid reabsorption in the pars convoluta of the juxtamedullary nephrons decreased to the same extent in segments obtained from unilaterally or bilaterally obstructed kidneys. Perfusion of thick ascending limbs of the loop of Henle revealed a marked impairment in their ability to decrease chloride concentration in the perfusate in segments obtained from unilaterally or bilaterally obstructed kidneys. Hanley and Davidson also examined the functional integrity of the cortical collecting tubule by determining the diffusion of tritium-labeled water in response to administration of antidiuretic hormone in vitro [73]. As compared to cortical collecting segments obtained from control animals, water diffusion in response to ADH was decreased in segments from unilaterally or bilaterally obstructed kidneys. These studies therefore indicate that intrinsic defects in reabsorption exist in certain nephron segments of the unilaterally and bilaterally obstructed kidney. Further, these defects were qualitatively and quantitatively similar in both models. Perhaps the differences between the two situations observed in micropuncture experiments relate to extrarenal events.

*Concentrating defect.* Patients with chronic obstructive nephropathy classically manifest an impaired ability to concentrate urine [74]. The magnitude of this defect, although quite variable, can be marked. In fact, polyuria is sometimes a presenting symptom of chronic obstructive uropathy [75–77]. Children with obstructive uropathy can develop profound dehydration and hypernatremia as a consequence of impaired reabsorption of free water.

Relief of obstruction in rats with either unilateral or bilateral ureteral obstruction produces an impaired ability to concentrate the urine [43, 44]; this defect is unresponsive to vasopressin administration. Depletion of the solute content of the papillary interstitium may be one important contributing factor [44]. This decrease in solute content after relief of obstruction appears to be perpetuated by a relative increase in blood flow to papillary structures [44]. That is, GFR of deep nephrons has been shown to be reduced by 50% to 60%, whereas inner medullary plasma flow either does not change from control levels during obstruction or increases slightly. A specific defect in collecting duct function has not been demonstrated but cannot be excluded [78]. In vivo studies in rats subjected to bilateral ureteral obstruction for 20 hours have revealed that injection of vasopressin after release of the obstruction fails to increase the excretion of cyclic AMP as it does in normal control rats [79]. These results indicate an impairment of vasopressin-dependent cyclic AMP production in postobstructed kidneys and suggest that the impairment in urinary concentrating ability observed following release of obstruction might relate, at least in part, to inhibition of vasopressin-dependent cyclic AMP production within the kidney [79, 80].

The sequence of events responsible for abnormal water reabsorption and for the concentrating defect after relief of obstruction may be as follows (Fig. 3). An increase in medullary prostaglandin synthesis may be responsible for the decreased reabsorption of sodium chloride by the medullary ascending limb of Henle's loop in vitro [81, 82]. Decreased reabsorption of sodium chloride in this segment decreases medullary solute content. Increased prostaglandin synthesis may lead to an increase in blood flow within the vasa recta and to persistent solute washout from the medulla. A decrease in solute content in the medulla decreases water efflux from the descending limb of Henle's loop and increases the amount of fluid delivered to the bend of the loop after relief of the obstruction [44]. This, in turn, may decrease the sodium chloride gradient necessary for passive sodium chloride efflux in the thin ascending limb of the loop [83]. A decrease in medullary solute content would decrease the diffusion of water out of the collecting duct. In addition, an increase in medullary prostaglandin production may antagonize the effect of vasopressin, thereby reducing the hydraulic permeability of the collecting tubule and contributing to the decrease in urine osmolality [84, 85].

*Acid-base balance and urinary acidification.* Serum bicar-

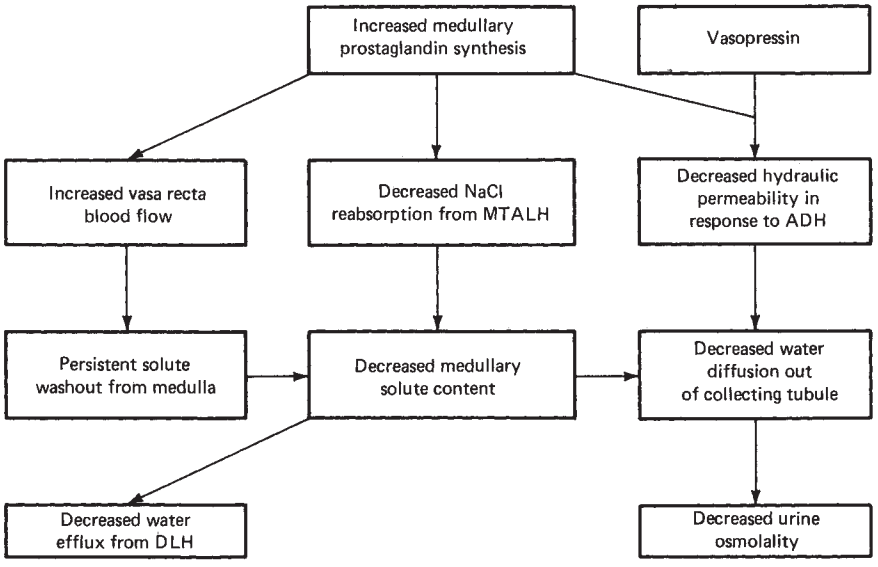


**Fig. 3.** *Potential mechanisms responsible for the renal concentrating defect observed after release of urinary tract obstruction* (DLH stands for descending loop of Henle; MTALH stands for medullary thick ascending loop of Henle).

bonate levels were substantially decreased in the patient we are discussing today. This decrease might reflect the renal insufficiency produced by bilateral ureteral obstruction. Following release of obstruction, plasma bicarbonate rose. Even on hospital day 9, when the GFR exceeded 60 ml/min, however, plasma bicarbonate remained at approximately 20 mEq/liter. This persistent decrease in plasma bicarbonate might have been related to administration of isotonic sodium chloride with little or no bicarbonate during the postobstructive diuresis, or it might be related to an acidifying defect that can occur in patients with urinary tract obstruction. Indeed, defects in acidification have been reported with either bilateral or unilateral ureteral obstruction [74, 86]. Earley described an infant with obstructive uropathy whose urine pH ranged between 6.3 and 6.9 when the arterial pH was 7.3 [77]. Berlyne described an acidifying defect in 6 of 7 patients with chronic hydronephrosis [74]. These patients did not acidify urine appropriately following an ammonium chloride load. Both ammonium excretion and titratable acid excretion were low. Recently, Batlle, Arruda, and Kurtzman characterized the acidifying defect in 13 patients which chronic obstructive uropathy [87]. All patients manifested a hyperkalemic metabolic acidosis. In all patients, excretion of ammonium and titratable acid either decreased or failed to respond to an acid load. Three defects were found. Five patients had a selective aldosterone deficiency. These patients acidified urine appropriately in response to an ammonium chloride load. The remaining patients either had classic distal renal tubular acidosis or a combined defect.

In relation to the findings in our patient, it should be noted that the acidification defect can persist after release of obstruction. Ericsson, Wineberg, and Zetterstrom described 6 children with postobstructive diuresis, 3 of whom had a high urine pH despite a normal or low plasma bicarbonate concentration [86]. Two mechanisms might account for the defect in the capacity of the postobstructed kidney to acidify urine. First, bicarbonate excretion might increase markedly. In a patient reported by Falls and Stacey, the urine pH remained consistently alkaline during the postobstructive period [64]. This alkaline diuresis was associated with a high rate of bicarbonate loss, but with normal ammonium and titratable acid excretion, the patient became acidotic. The magnitude of the bicarbonate leak suggested that the site of altered bicarbonate reabsorption during the diuretic phase was the proximal tubule. Further, bicarbonate reabsorption in the distal segments was markedly reduced. To my knowledge, no studies have characterized the maximal rates of bicarbonate reabsorption in this state, or the bicarbonate delivery out of the proximal tubule when plasma bicarbonate levels were in the normal range.

Second, considerable evidence suggests an impairment in the intrinsic capacity of the kidney to acidify urine at distal sites. This defect is most apparent after release of unilateral ureteral obstruction. Better et al reported that, in a patient with unilateral ureteral obstruction, the urine pH from the postobstructed kidney was always more alkaline than that of the contralateral, normally functioning kidney [71]. The postobstructed kidney failed to acidify urine appropriately during ammonium chloride loading. Titratable acid excretion by this kidney was low, even when values were corrected for the reduction in GFR. This decrease in titratable acid excretion was in part a consequence of the low rate of phosphate excretion. The acidification defect that occurs after release of unilateral ureteral obstruction has been examined in the rat and the dog. Walls et al reported that following the release of unilateral ureteral obstruction, bicarbonate reabsorption along the portions of the proximal and distal tubule accessible to micropuncture increased despite both absolute and fractional bicarbonate excretion being significantly greater from the obstructed kidney than from the contralateral kidney [88]. Bicarbonate titration studies revealed similar reabsorptive rates for the obstructed and contralateral control kidney. Values for urine $PCO_2$ during bicarbonate loading were considerably less in the postobstructed than in the contralateral kidney; this finding indicated an impaired capacity of the distal nephron to secrete hydrogen. Thirakomen and coworkers confirmed these observations in the dog and noticed also that urine

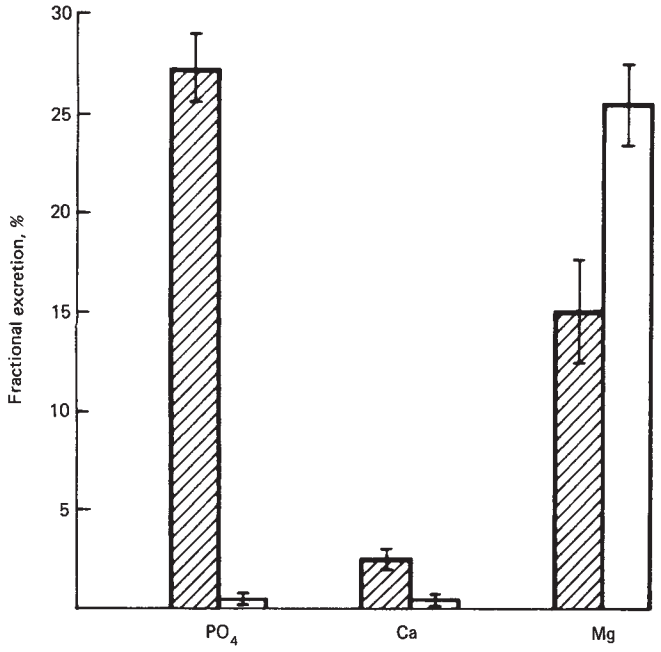


**Fig. 4.** *Fractional excretion of phosphate, calcium and magnesium by the contralateral control kidney* (hatched bars) *and the postobstructed kidney* (clear bars) *of rats following unilateral ureteral obstruction.* The differences in fractional excretion between the two kidneys were significant (<0.001) for the three substances studied.

and blood $PCO_2$ measurements obtained during phosphate and bicarbonate infusion were reduced [89]. These studies indicate that the ability of surface nephrons to secrete hydrogen ions is intact, and that the alteration in acidification that occurs after release of unilateral obstruction results from a defect in either the collecting duct or in deep nephrons.

*Magnesium excretion after relief of urinary tract obstruction.* In the patient under discussion, serum magnesium concentration fell from 1.9 mg/dl two days prior to the release of obstruction to 0.7 mg/dl the day after insertion of the nephrostomy. This decrease in serum magnesium probably was related to profound losses of magnesium in the urine after relief of obstruction.

Magnesium excretion increases inappropriately after release of both bilateral and unilateral ureteral obstruction. As with calcium, urinary loss of magnesium can be striking following release of bilateral obstruction [64, 90] and occasionally causes profound magnesium deficiency [91]. The increase in magnesium excretion seems to parallel the increase in sodium excretion that occurs during the postobstructive diuretic phase [64, 90]. Unlike calcium, magnesium excretion is high following release of unilateral obstruction (Fig. 4). Better et al found that fractional and absolute magnesium excretion were significantly greater from the postobstructed kidney than from the normally functioning kidney after release of unilateral ureteral obstruction in one patient [71]. Purkerson, Slatopolsky, and I reported a similar alteration in renal magnesium handling in rats [92]. This effect was not altered by dietary magnesium restriction. Because the intrinsic reabsorptive capacity of the thick ascending limb of Henle decreases during unilateral ureteral obstruction, we postulated that the differences in magnesium and calcium excretion in the urine after release of obstruction resulted from preferential reabsorption of calcium in the proximal tubule and from magnesium in the ascending limb of the loop of Henle [92].

*Phosphate excretion after relief of urinary tract obstruction.* In the patient under discussion, the serum level of inorganic phosphate was 7.4 mg/dl two days prior to the relief of obstruction. The serum phosphate level fell to 2 mg/dl the day after placement of the nephrostomy, to 1.9 two days after, and to 1.7 mg/dl six days after. This decrease in the serum phosphate concentration very likely was due to a marked loss of phosphorus in the urine.

After release of ureteral obstruction, phosphate handling by the kidney depends on two factors: whether the obstruction is bilateral or unilateral, and duration of the obstruction. Absolute and fractional excretion of phosphate increases after release of bilateral ureteral obstruction [64, 90]. In a case reported by Falls and Stacey [64], phosphate excretion was 76.6% of the filtered load at the peak of diuresis and fell to 53.1% of the filtered load of phosphate in the final hour of study. Absolute phosphate excretion declines, coincident with the decrease in sodium and water excretion. The fractional excretion of phosphate partially depends on whether an individual regains normal renal function. If GFR does not return to normal, fractional phosphate excretion increases as required for maintenance of phosphate balance.

Although renal phosphate handling in the postobstructive period has been extensively studied in experimental models [92–96], the mechanisms responsible for the phosphaturia remain unclear. Beck reported that absolute and fractional excretion of phosphate rose strikingly in the rat after release of bilateral obstruction that had been present for 24 hours [96]. This increased phosphate excretion could not be accounted for by changes in the extracellular fluid volume. When these rats were phosphate restricted, and plasma levels of phosphate were low prior to obstruction, phosphate excretion did not increase after release of ureteral obstruction. When plasma phosphate levels were increased in normal controls to levels equal to those in the obstructed group, phosphate excretion was similar in the two groups. These studies suggest that renal phosphate handling after release of bilateral ureteral obstruction somehow depends on alterations in the filtered phosphate load. Although no studies have directly assessed the site of the nephron where phosphate reabsorption is suppressed in obstructive uropathy, the magnitude of the increase in phosphate excretion and the fact that the major site for phosphate reabsorption lies in the proximal tubule suggest that this latter segment must be the major site of altered reabsorption.

The mechanisms involved in the altered phosphate handling that occurs during the diuretic phase have been determined in studies performed following release of unilateral ureteral obstruction. In humans, phosphate excretion from the postobstructed kidney is consistently and markedly reduced after release of unilateral obstruction [71, 72]. The decrease in phosphate excretion is out of proportion to the reduction in the filtered load. Thus, fractional phosphate excretion falls markedly, whereas phosphate excretion from the normally functioning kidney actually increases. These alterations in phosphate handling in humans also have been reproduced in the rat [93] and the dog [94, 95]. Purkerson et al showed that the increase in

phosphate excretion from the contralateral kidney can be abolished by parathyroidectomy [93]. Phosphate excretion by the postobstructed kidney increased only modestly when parathyroid hormone was given in large amounts, however [71]. Further, cAMP excretion in the obstructed kidney, when expressed per milliliter of GFR, did not differ from that in the contralateral kidney.

The effect of unilateral ureteral obstruction on phosphate excretion can be reproduced in normal animals by aortic constriction. In this latter setting, phosphate excretion does not increase after the administration of parathyroid hormone. These studies suggest that the decreased phosphate excretion that occurs after release of unilateral ureteral obstruction is due to a fall in GFR per nephron and to an increase in phosphate reabsorption along the proximal segments of the nephron [93]. The concept that phosphate reabsorption is increased in the proximal tubule is supported by micropuncture studies demonstrating enhanced fluid reabsorption in this segment of the nephron [42, 44]. The available data suggest that altered phosphate handling after release of unilateral ureteral obstruction results from altered renal hemodynamics and is not a consequence of an intrinsic defect in proximal tubular function, and further that the marked increase in phosphate excretion following release of bilateral ureteral obstruction is a result of extrarenal factors. Weinreb et al supported this view in studies of phosphate handling by membrane vesicles prepared from luminal membranes of proximal tubules obtained from postobstructed kidneys [94]. The findings indicate that the intrinsic capacity of the luminal membrane of the proximal tubule to reabsorb phosphorus and to respond to parathyroid hormone is unaltered following ureteral obstruction of 24 hours duration.

*Summary.* The changes in intratubular pressure, renal blood flow, and glomerular filtration that occur during obstruction represent a complex picture of alterations of interdependent renal functions. Experimental studies in animals with obstruction have provided substantial information about the sequence of events and mechanisms underlying the derangements observed. Some of these variations are a direct consequence of impaired urine flow; others might be the result of changes in the levels of intrarenal hormones such as prostaglandins, angiotensin, and catecholamines. As our knowledge regarding the role played by these vasoactive substances in obstructive nephropathy increases, the mechanisms underlying some of the alterations observed will come into clearer focus and allow for the rational development of still more successful therapeutic interventions.

### Questions and answers

DR. RAMZI COTRAN (*Chairman, Department of Pathology, Brigham and Women's Hospital, Boston*): Most of the experiments that you cited on the role of prostaglandins and thromboxane come from indirect experiments using inhibitors. Have there been any studies in this experimental model with direct measurements of biosynthetic processes on, say, whole glomeruli or tissue slices?

DR. KLAHR: In the rabbit, unilateral ureteral occlusion causes an increase in basal levels of prostaglandin $E_2$ biosynthesis as well as in the responsiveness of $PGE_2$ synthesis to stimulatory agents, such as bradykinin, angiotensin II, and norepinephrine, in the obstructed kidney perfused in vitro when compared with the contralateral kidney of the same animal or a perfused kidney from a normal rabbit [97]. Of some interest was the finding that increased prostaglandin production could be demonstrated in a strain of rats (MRC/H) with congenital hydronephrosis. Morrison et al also showed that the experimental kidney of rabbits with unilateral ureteral obstruction had an increased capacity for thromboxane $A_2$ biosynthesis [53, 54]. It should be noted that whereas in the rabbit the "obstructed" kidney produces increased amounts of basal and peptide hormone-stimulated thromboxane $A_2$, in the cat unilateral ureteral obstruction does not lead to increased production of thromboxane $A_2$ by the experimental kidney [98]. On the other hand, the production of thromboxane $A_2$ is increased in microsomal preparations obtained from hydronephrotic kidneys of humans.

Turning to the question of synthesis of prostaglandins or thromboxanes by whole glomeruli or tissue slices, Folkert and Schlondorff recently demonstrated that isolated glomeruli obtained from both kidneys of rats with unilateral ureteral obstruction showed no differences in the rates of synthesis of thromboxane or prostaglandins after 24 hours of obstruction [99]. After 72 hours of obstruction, however, the synthesis of thromboxane, $PGF_{2\alpha}$, and 6-keto-$PF_{1\alpha}$ was greater in glomeruli isolated from the obstructed kidney. Whinnery, Shaw, and Beck have shown increased synthesis of thromboxane and $PGE_2$ by papillary slices obtained from the experimental kidney of rats with unilateral ureteral ligation [100]. In cortical slices, obstruction had a stimulatory effect on thromboxane production but not on $PGE_2$ production.

DR. BARRY BRENNER (*Director, Renal Division, Brigham and Women's Hospital, Boston*): Dr. Klahr, I have two questions. First, insofar as prostaglandin biosynthesis in the kidney is highly compartmentalized, do you suppose that the defect in urinary concentrating ability following obstruction is due to excessive E series production in the medulla and papilla, whereas the defects in glomerular perfusion and filtration are the result of preferential $PGI_2$ and thromboxane biosynthesis in predominantly cortical structures, especially glomeruli? Turning to my second question, since all glomeruli might not resume function concomitantly following release of obstruction, what factors influence the time course of recovery?

DR. KLAHR: Regarding your first question, circumstantial evidence indicates that the defect in urinary concentrating ability probably is related to increased synthesis of prostaglandin $E_2$ in the medulla and perhaps papilla of the obstructed kidney. Whether altered synthesis of other prostaglandins in the medulla also contributes to the concentrating defect is not known. The mechanisms responsible for the decrease in glomerular perfusion and filtration occurring after 12 to 24 hours following the onset of obstruction are not well understood. The action of vasoconstrictor substances might predominate in glomerular arterioles. This predominance of a vasoconstrictor effect might be due to: *(1)* increased production of vasoconstrictor substances in the cortex (thromboxane, catecholamines, angiotensin II); *(2)* decreased production of vasodilators (prostacyclin and perhaps $PGE_2$); *(3)* a combination of 1 and 2; or *(4)* an altered response of the afferent arteriole to a given level of vasoconstrictors (increased response) or vasodilators (decreased response).

In relation to your question about factors that influence the

time course of recovery of renal function after release of obstruction, let me point out that the duration of obstruction per se plays an important role. If the obstruction persists for longer than 72 or 96 hours, loss of renal function usually is permanent even after the obstruction is relieved. With shorter periods of obstruction, recovery of function is complete in experimental animals. However, in the rat it can take up to 6 days for GFR to return to normal values after relief of bilateral obstruction that had lasted 30 hours [46]. There is also evidence in the model of unilateral ureteral obstruction in the rat that cortical vasoconstriction persists for 3 hours after relief of obstruction, with surface nephrons exhibiting a greater decrease in single-nephron GFR than do deep nephrons [44]. I am not aware of any studies that have examined in a sequential fashion the mechanisms underlying the recovery of renal function that occurs after short periods of obstruction. It is not clear whether recovery of GFR values to preobstructive levels represents normal function of the full complement of nephrons in the postobstructed kidney or whether it indicates the presence of nephron heterogeneity with some nephrons exhibiting hyperfiltration and others decreased GFR per nephron. It is obvious that in the clinical setting other factors such as degree of obstruction (complete or partial), site of the obstruction, and the presence or absence of infection influence the time course of recovery of renal function.

DR. JORDAN J. COHEN: Dr. Klahr, you have indicated that increased prostaglandin synthesis within the kidney may mediate some of the important changes in function induced by obstruction. The question still remains, what is it about obstruction that "turns on" prostaglandins?

DR. KLAHR: In animals with persistent obstruction, unilateral ureteral ligation leads to an increase in the activities of phosphatide acylhydrolase [101] and cyclooxygenase [102]. The first of these enzymes is responsible for the release of free arachidonic acid from the phospholipid pool; the cyclooxygenase is responsible for the subsequent metabolism of arachidonic acid to endoperoxides and the different prostaglandins. Administration of protein synthesis inhibitors prevents the increase in the activities of these two enzymes that occurs with obstruction. This finding suggests de novo synthesis during obstruction of two of the key enzymes involved in prostaglandin production. The early events that trigger prostaglandin release after the onset of obstruction are not known, however. Because changes in interstitial pressure alone are not sufficient to elicit the type of vasodilation produced by ureteral obstruction, the release of prostaglandins in this setting probably depends in some way on elevated pressures in renal tubules or perhaps in Bowman's space.

DR. BRENNER: Do you know of any experiments using captopril or renin antibodies in obstruction to elucidate the role of angiotensin?

DR. KLAHR: Most studies indicate that the increased release of renin, and presumably angiotensin, from the obstructed kidney follows the initial increase in prostaglandin synthesis. Maneuvers designed to modify the renal hemodynamic effects of obstruction, such as prior salt loading to deplete renin stores in the kidney, or the infusion of saralasin, an antagonist of angiotensin II, had no effect on renal function in this setting. But as I mentioned before, Yarger, Schocken, and Harris found that administration of captopril led to improved renal hemodynamics during obstruction [55].

DR. DAVID BERNARD (*Director of Clinical Nephrology, University Hospital, Boston*): Dr. Klahr, would you return for a moment to the role that neurogenic influences might be playing? As you know, it has been shown that when ureteral pressure is increased in one kidney, the early phase of ipsilateral renal vasodilation is associated with contralateral vasoconstriction, which can be abolished by renal denervation. Have the early and late changes in renal blood flow or in prostaglandin production that follow ureteral obstruction been examined in the denervated state or after the administration of alpha- or beta-adrenergic receptor blockers or both?

DR. KLAHR: Afferent nerve activity increases when ureteral pressure is elevated [103]. Evidence also indicates that the compensatory vasoconstriction occurring in the normal kidney during unilateral ureteral ligation is mediated by increased nerve activity [60] and that renal nerve activity contributes to the vasoconstriction occurring after 24 hours of unilateral ureteral obstruction [58]. Transection of the spinal cord abolishes the hemodynamic changes that occur in the contralateral kidney when unilateral ureteral obstruction is produced. Thus, a central type of reflex is responsible for the changes that occur in the contralateral kidney after unilateral ureteral obstruction. Glomerular filtration rate, renal blood flow, urine flow, and sodium excretion all increase significantly with acute denervation after relief of unilateral ureteral obstruction, but no such response occurs in kidneys with bilateral ureteral obstruction that are undergoing a postobstructive diuresis [104]. Renal tissue catecholamines are markedly decreased in the kidneys of animals with bilateral ureteral obstruction but are normal in the experimental kidneys of rats with unilateral obstruction. I am not aware of any studies that have examined the effects of chronic obstruction on nerve activity or the consequences of alpha- or beta-adrenergic blockade on the hemodynamic changes produced by obstruction.

DR. JEROME P. KASSIRER: Dr. Klahr, what data are available in patients about the relation between the duration and extent of obstruction on the one hand and the degree of recovery of renal function on the other? How soon after the onset of partial or complete obstruction does one have to intervene to preserve kidney function?

DR. KLAHR: This is a very difficult question to answer based on the information available in patients. I mentioned already the information that exists in experimental animals. In patients, there are only isolated case reports. For example, Better et al described a patient who had unilateral ureteral obstruction for 3 months as a consequence of a surgical procedure [71]. When the obstruction was discovered and relieved, the creatinine clearance of the postobstructed kidney measured immediately after release was about 2 ml/min. Over the next few weeks, this value increased to approximately 10 ml/min. This level of renal function would have been enough to sustain life without any difficulty if this were a solitary kidney. It is also clear that this patient did not regain complete recovery of function in the postobstructed kidney. The contralateral kidney, as I recall, had a GFR of about 60 ml/min, which presumably was also the level of function in the affected kidney prior to obstruction.

An attempt has been made to use renal scanning to predict recovery of renal function in obstruction. Recovery of renal

function after chronic obstruction has been observed in patients who show no function on renal scan [105, 106]. McAfee, Singh, and O'Callaghan reported that in 42 patients, neither excretory urography nor renal imaging could predict the degree of recovery of renal function after obstruction was relieved [107]. On the other hand, Gillenwater, Teates, and Marion found excellent correlation in predicting recovery of function using $^{131}$I-hippuran renal scan in dogs (personal communication). Dogs were obstructed for 2, 4, or 6 weeks. The recovery rate was 39% after 2 weeks, 10% after 4 weeks, and 2% after 6 weeks of obstruction. In every case, the renogram (before release of the ureteral obstruction), evaluated visually and by partition coefficients, predicted the degree of recovery of that kidney as measured by inulin and PAH clearances. Other means of assessing recoverability include the placement of temporary nephrostomy tubes with monitoring of PAH clearances, and the use of intravenous urograms using the width of the cortex and the degree of function as the index.

Regarding the second part of your question, there is a greater urgency to intervene if the obstruction is complete instead of partial or if complications such as infection are present. Certainly, in most patients with renal stones and partial obstruction, it might be prudent to wait for spontaneous passage of the calculi, in the absence of complications. When infection, costovertebral angle tenderness, or other complications are present, the obstruction should be relieved promptly.

DR. COHEN: The concentrating defect, as you indicated, is often the most striking clinical event during the postobstructive phase. You cited evidence that this defect may be related both to a decrease in medullary solute content and to an intrinsic problem with hydroosmotic water flow through the collecting duct. Is it known to what extent these changes reflect abnormalities in the adenylate cyclase-receptor mechanism for ADH?

DR. KLAHR: It is known that ADH not only increases the hydroosmotic permeability to water and urea of the cortical [108] and medullary collecting duct [109] but also increases the reabsorption of sodium chloride in the medullary thick ascending limb of Henle's loop [110]. There is evidence to suggest that both of these effects of ADH may be mediated via cyclic AMP. It has been shown in the toad bladder that prostaglandins interfere with the hydroosmotic effect of ADH but do not block the increased water flow in response to cyclic AMP. Such evidence would suggest that in some way prostaglandins inhibit the action of ADH at the level of the adenylate cyclase. I am not aware of any studies that have examined the effect of prostaglandins on the binding of ADH to its receptor. Preliminary evidence indicates that excessive prostaglandin production in obstruction may inhibit the effects of other hormones, such as PTH, on the kidney, presumably by interfering not with the binding of the hormone to its receptor but by modifying the response of the adenylate cyclase to the hormone-receptor complex.

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